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(21) International Application Number: PCT/GB95/02849 (22) International Filing Date: 6 December 1995 (06.12.95) (30) Priority Data: 9424553.7 6 December 1994 (06.12.94) GB 9425971.0 22 December 1994 (22.12.94) GB 9502865.0 14 February 1995 (14.02.95) GB (71) Applicant (for all designated States except US): AGREVO UK LIMITED [GB/GB]; Hauxton, Cambridge CB2 5HU (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): DÖLLER, Uwe [DE/DE]; Rembrandtring 24a, D-63110 Rodgau (DE). BRAUN, Peter [DE/DE]; Rektor-Roth-Strasse 2A, D-55268 Nieder-Olm (DE). SACHSE, Burkhard [DE/DE]; An der Ziegelei 30, D-65779 Kelkheim (DE). REISSEL, Willy [DE/DE]; Geisenheimer Strasse 88, D-60529 Frankfurt am Main (DE). ORT, Oswald, Peter, Gerald [DE/GB]; Chesterford Park, Saffron Walden, Essex CB10 1XL (GB). HOUGH, Thomas, Lawley [GB/GB]; Chesterford Park, Saffron Walden, Essex CB10 1XL (GB). SIMPSON, Donald, James [GB/GB]; Chesterford Park, Saffron Walden, Essex CB10 1XL (GB).		LINDNER, Kerstin [DE/GB]; Chesterford Park, Saffron Walden, Essex CB10 1XL (GB). LINDELL, Stephen, David [GB/GB]; Chesterford Park, Saffron Walden, Essex CB10 1XL (GB). (74) Agent: WALDMAN, Ralph, David; AgrEvo UK Limited, Patent Dept., Chesterford Park, Saffron Walden, Essex CB10 1XL (GB). (81) Designated States: AU, BG, BR, CA, CN, CZ, FI, HU, JP, KR, KZ, MX, NO, NZ, PL, RO, RU, SD, SK, UA, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG). Published <i>With international search report.</i>
(54) Title: HETEROCYCLYL SUBSTITUTED HYDROXYACETAMIDE DERIVATIVES AS FUNGICIDES (57) Abstract <p>Compounds of formula (I) wherein Q is optionally substituted heterocyclyl; Z is optionally substituted hydroxy or mercapto; E is (i) CO-N(R²), (ii) CS-N(R²) or (iii) C(SR²) = N; W is O, N(R³), optionally substituted methylene or ethylene; R¹, R² and R³ are phenyl or alkyl, each of which is optionally substituted, or hydrogen; Y is phenyl, heteroaryl or alkyl, each of which is optionally substituted, or hydrogen; and when W is O or N(R³), and/or E is (ii) or (iii), Y is also optionally substituted phenyl, have fungicidal activity.</p> <div style="text-align: center; margin-top: 20px;"> $\begin{array}{c} \text{Z} \\ \\ \text{Q} - \text{C} - \text{E} - \text{W} - \text{Y} \\ \\ \text{R}^1 \end{array} \quad (\text{I})$ </div>		

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HETEROCYCLYL SUBSTITUTED HYDROXYACETAMIDE DERIVATIVES AS FUNGICIDES

5 Field of the invention

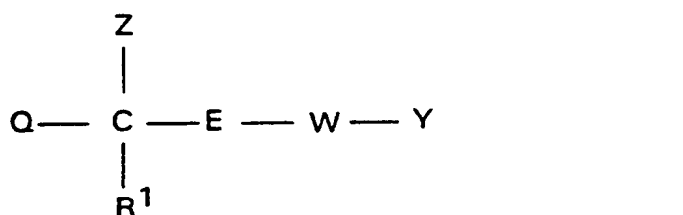
This invention relates to new derivatives of mandelic acid useful as fungicides.

Prior art

Substituted arylacetamides are described as active components in herbicides (JP
10 58/032853) and as compositions for treating skin diseases (EP 98743).

Disclosure of the invention

According to the invention there is provided the use for combating
phytopathogenic fungi, of a compound of formula I



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wherein

Q is optionally substituted heterocyclyl;

Z is optionally substituted hydroxy or mercapto;

E is (i) CO--N(R²), (ii) CS--N(R²) or (iii) C(SR²)=N

20 W is O, N(R³), optionally substituted methylene or ethylene;

R¹, R² and R³ are phenyl or alkyl, each of which is optionally substituted, or
hydrogen;

Y is phenyl, heteroaryl or alkyl, each of which is optionally substituted, or
hydrogen;

25 and when W is O or N(R³), and/or E is (ii) or (iii), Y is also optionally substituted
phenyl, together with salts and complexes with metal salts.

Most of the compounds are novel and the invention includes compounds of
general formula I as defined above with the exception that when E is defined as in

30 (i), W is NH, R¹ is H and Y is hydrogen, then Q is substituted.

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Substituents when present on any phenyl or heterocyclyl group, or on A, include for example halogen, cyano or nitro, or the group D-(L)_m-, where m is 0 or 1, L is O, S, SO₂, CO or O-CO and D is alkyl, cycloalkyl, cycloalkenyl, alkenyl, alkynyl, phenyl, heterocyclyl or amino, (each of which is optionally substituted) or when m

5 is 1 can also be hydrogen; or two adjacent groups on the ring together with the atoms to which they are attached can form an homo or hetero ring which may be similarly substituted as for phenyl.

Z is preferably unsubstituted, but optional substituents include for example those

10 defined under D or acyl.

When W is substituted methylene or ethylene, substituents include for example those defined under D or acyl., but are usually alkyl, especially methyl.

15 The term heterocyclyl includes both aromatic and non-aromatic heterocyclyl groups. Heterocyclyl groups are generally 5, 6 or 7-membered rings containing up to 4 hetero atoms selected from nitrogen, oxygen and sulfur. Examples of heterocyclyl groups are furyl, thienyl, pyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, dioxolanyl, oxazolyl, thiazolyl, imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl,

20 pyrazolinyl, pyrazolidinyl, isoxazolyl, isothiazolyl, oxadiazolyl, triazolyl, thiadiazolyl, pyranyl, pyridyl, piperidinyl, dioxanyl, morpholino, dithianyl, thiomorpholino, pyridazinyl, pyrimidinyl, pyrazinyl, piperazinyl, triazinyl, thiazolinyl, benzimidazolyl, tetrazolyl, benzoxazolyl, imidazopyridinyl, 1,3-benzoxazinyl, 1,3-benzothiazinyl, oxazolopyridinyl, benzofuranyl, quinolinyl, quinazolinyl, quinoxalinyl, sulfolanyl,

25 dihydroquinazolinyl, benzothiazolyl, phthalimido, benzofuranyl, azepinyl, oxazepinyl, thiazepinyl, diazepinyl and benzodiazepinyl.

Alkyl groups are preferably of 1 to 8, e.g. 1 to 6, carbon atoms. Alkenyl and alkynyl groups are generally of 3 to 6 carbon atoms. Cycloalkyl or cycloalkenyl

30 groups are preferably of 3 to 8 carbon atoms.

Substituents, when present on any alkyl, cycloalkyl, cycloalkenyl, alkenyl or alkynyl moiety include halogen, azido, cyano, optionally substituted alkoxy, optionally substituted alkylthio, hydroxy, nitro, optionally substituted amino, acyl,

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acyloxy, optionally substituted phenyl, optionally substituted heterocyclyl, optionally substituted phenoxy and optionally substituted heterocyclyl.

Cycloalkyl or cycloalkenyl groups may also be substituted by alkyl.

5

Amino groups may be substituted for example by one or two optionally substituted alkyl or acyl groups, or two substituents can form a ring, preferably a 5 to 7-membered ring, which may be substituted and may contain other hetero atoms, for example morpholine, thiomorpholine, or piperidine.

10

The term acyl includes the residue of sulfur and phosphorus-containing acids as well as carboxylic acids. Examples of acyl groups are thus $-\text{COR}^5$, $-\text{COOR}^5$, $-\text{CXNR}^5\text{R}^6$, $-\text{CON}(\text{R}^5)\text{OR}^6$, $-\text{COONR}^5\text{R}^6$, $-\text{CON}(\text{R}^5)\text{NR}^6\text{R}^7$, $-\text{COSR}^5$, $-\text{CSSR}^5$, $-\text{S}(\text{O})_p\text{R}^5$, $-\text{S}(\text{O})_2\text{OR}^5$, $-\text{S}(\text{O})_p\text{NR}^5\text{R}^6$, $-\text{P}(=\text{X})(\text{OR}^5)(\text{OR}^6)$, $-\text{CO}-\text{COOR}^5$, where R^5 , R^6 and R^7 which may be the same or different, are hydrogen, optionally substituted alkyl, optionally substituted cycloalkyl, optionally substituted cycloalkenyl, optionally substituted alkenyl, optionally substituted alkynyl, optionally substituted phenyl or optionally substituted heterocyclyl or R^6 and R^7 together with the atom(s) to which they are attached can form a ring, p is 1 or 2 and X is O or S.

20

Salts of compounds of the invention are usually those of agriculturally acceptable metal cations or organic bases, especially tertiary amines.

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Complexes of compounds of the invention are usually formed from a salt of formula MAN_2 , in which M is a divalent metal cation, e.g. copper, manganese, cobalt, nickel, iron or zinc and An is an anion, e.g. chloride, nitrate, sulfate or acetate.

30

The compounds of the invention have activity as fungicides, especially against fungal diseases of plants, e.g. mildews and particularly barley powdery mildew (*Erysiphe graminis*) and vine downy mildew (*Plasmopara viticola*), rice blast (*Pyricularia oryzae*), cereal eyespot (*Pseudocercospora herpotrichoides*), rice sheath blight (*Pellicularia sasakii*), grey mould (*Botrytis cinerea*), damping off (*Rhizoctonia solani*), wheat brown rust (*Puccinia recondita*), late tomato or potato

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blight (*Phytophthora infestans*), apple scab (*Venturia inaequalis*), glume blotch (*Leptosphaeria nodorum*). Other fungi against which the compounds may be active include other powdery mildews, other rusts, and general pathogens of Deuteromycete, Ascomycete, Phycomycete and Basidiomycete origin.

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The compounds of the invention are generally formulated in conventional compositions used for fungicides. These compositions can contain one or more additional pesticides, for example compounds known to possess herbicidal, fungicidal, insecticidal, acaricidal or nematocidal properties.

10

The diluent or carrier in the composition of the invention can be a solid or a liquid optionally in association with a surface-active agent, for example a dispersing agent, emulsifying agent or wetting agent. Suitable surface-active agents include anionic compounds such as a carboxylate, for example a metal carboxylate of a

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long chain fatty acid; an N-acylsarcosinate; mono- or di-esters of phosphoric acid with fatty alcohol ethoxylates or salts of such esters; fatty alcohol sulfates such as sodium dodecyl sulfate, sodium octadecyl sulfate or sodium cetyl sulfate; ethoxylated fatty alcohol sulfates; ethoxylated alkylphenol sulfates; lignin sulfonates; petroleum sulfonates; alkyl-aryl sulfonates such as alkyl-benzene

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sulfonates or lower alkylnaphthalene sulfonates, e.g. butyl-naphthalene sulfonate; salts of sulfonated naphthalene-formaldehyde condensates; salts of sulfonated phenol-formaldehyde condensates; or more complex sulfonates such as the amide sulfonates, e.g. the sulfonated condensation product of oleic acid and N-methyl taurine or the dialkyl sulfosuccinates, e.g. the sodium sulfonate of dioctyl

25

succinate. Nonionic agents include condensation products of fatty acid esters, fatty alcohols, fatty acid amides or fatty-alkyl- or alkenyl-substituted phenols with ethylene oxide, fatty esters of polyhydric alcohol ethers, e.g. sorbitan fatty acid esters, condensation products of such esters with ethylene oxide, e.g.

30

polyoxyethylene sorbitan fatty acid esters, block copolymers of ethylene oxide and propylene oxide, acetylenic glycols such as 2,4,7,9-tetramethyl-5-decyne-4,7-diol, or ethoxylated acetylenic glycols. Examples of a cationic surface-active agent include, for instance, an aliphatic mono-, di-, or polyamine as an acetate, naphthenate or oleate; an oxygen-containing amine such as an amine oxide or polyoxyethylene alkylamine; an amide-linked amine prepared by the

5

condensation of a carboxylic acid with a di- or polyamine; or a quaternary ammonium salt.

The compositions of the invention can take any form known in the art for the
5 formulation of agrochemicals, for example, a solution, a dispersion, an aqueous emulsion, a dusting powder, a seed dressing, a fumigant, a smoke, a dispersible powder, an emulsifiable concentrate or granules. Moreover it can be in a suitable form for direct application or as a concentrate or primary composition which requires dilution with a suitable
10 quantity of water or other diluent before application.

As a dispersion, the composition comprises a compound of the invention dispersed in a liquid medium, preferably water. It is often convenient to supply the consumer with a primary composition which can be diluted with water to form a
15 dispersion having the desired concentration. The primary composition can be provided in any one of the following forms. It can be a dispersible solution which comprises a compound of the invention dissolved in a water-miscible solvent with the addition of a dispersing agent. A further alternative comprises a compound of the invention in the form of a finely ground powder in association with a
20 dispersing agent and intimately mixed with water to give a paste or cream which can if desired be added to an emulsion of oil in water to give a dispersion of active ingredient in an aqueous oil emulsion.

An emulsifiable concentrate comprises a compound of the invention dissolved in a
25 water-immiscible solvent together with an emulsifying agent and which is formed into an emulsion on mixing with water.

A dusting powder comprises a compound of the invention intimately mixed with a solid pulverulent diluent, for example, kaolin.

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A granular solid comprises a compound of the invention associated with similar diluents to those which may be employed in dusting powders, but the mixture is granulated by known methods. Alternatively it comprises the active ingredient

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adsorbed or absorbed on a pre-granular diluent, for example, Fuller's earth, attapulgite or limestone grit.

5 A wettable powder usually comprises the active ingredient in admixture with a suitable surfactant and an inert powder diluent such as china clay.

Another suitable concentrate, particularly when the product is a solid, is a flowable suspension concentrate which is formed by grinding the compound with water, a wetting agent and a suspending agent.

10

The concentration of the active ingredient in the composition of the present invention is preferably within the range of 1 to 30 per cent by weight, especially 5 to 30 per cent by weight. In a primary composition the amount of active ingredient can vary widely and can be, for example, from 5 to 95 per cent by weight of the composition.

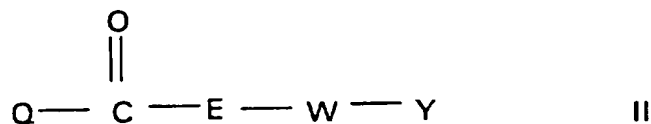
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The compounds of the invention may be prepared in known manner.

For example compounds where E is defined as under (i) may be obtained by

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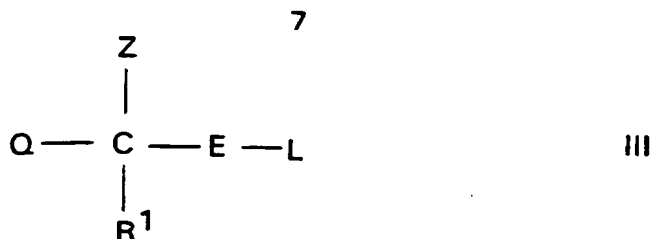
a) reducing a compound of formula II



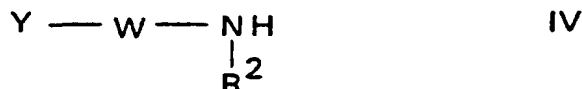
This reaction gives a compound where R¹ is H and Z is OH. The reduction is generally carried out using a reducing agent, especially a metal hydride e.g. lithium aluminium hydride or lithium borohydride, or diborane. These reactions are generally carried out in a solvent, preferably a polar solvent, such as an alcohol, e.g. methanol, ethanol or propanol, an ether or water or mixtures of these.

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b) by reacting a compound of formula III



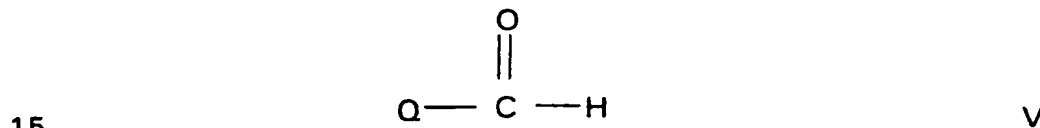
wherein L is hydroxy or a leaving group, e.g. a halogen, especially chlorine, or an ester forming group, e.g. alkoxy, with an amine of formula IV



- 5 Conventional peptide coupling conditions may be used e.g. using a mixture of N-hydroxysuccinimide and dicyclohexylcarbodiimide, especially when L is hydroxy.

The amines of formula IV can be obtained in known manner as described for example in Bull. Chem. Soc. Jap. 1990, 63, 1252; Angew. Chem. 1989, 101, 202 and 1992, 104, 914; Heterocycles, 1987, 26, 1595 and J. Med. Chem. 1971, 14, 322, 1988, 31, 1282, 1981, 24, 1063 and 1980, 23, 990 and USP 3,847,950.

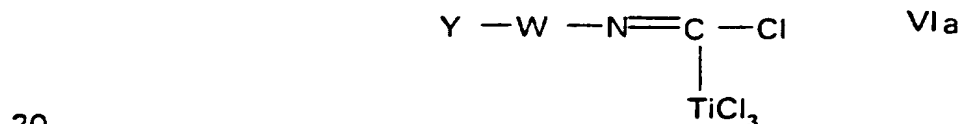
c) by a Passerini reaction, in which a compound of formula V



is reacted with a compound of formula VI



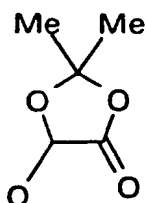
The reaction can take place in the presence of a mineral or carboxylic acid or be carried out via an intermediate of formula VIa



obtained by reacting the compound of formula IV with titanium tetrachloride.

c) by reacting a compound of formula VII

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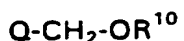


VI

with the amine of formula IV,

d) by reacting a compound of formula VIII

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VIII

where R¹⁰ is hydrogen or alkyl, first with carbon dioxide in the presence of tert.-butyllithium followed by reaction with a compound of formula IX

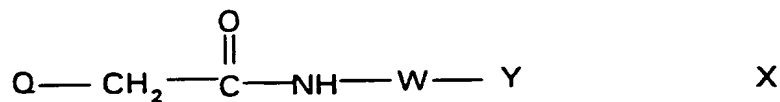


IX

under basic conditions, e.g. in the presence of tert.-butyllithium.

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e) by reacting a compound of formula X:



with a strong base, usually two equivalents, e.g. lithium diisopropylamide, followed by a halogenating agent, e.g. N-bromosuccinimide, or an oxygenating agent, e.g. lead tetraacetate.

The compounds of formula II to X are either known or can be prepared in known manner.

20 For example compounds of formula II can be prepared in a similar manner to process b) using a compound of formula IIa

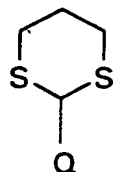


Compounds of formula III and IIIa can be obtained by methods described in for example Heterocycles, 1985, 23, 585, Heterocycles, 1985, 23, 1645, J. Org.

25 Chem. 1977, 42, 1089, J. Org. Chem. 1991, 56, 2937, Tetrahedron, 1982, 38, 1447, Tet. Letts. 1987, 28, 3971, J. Chem. Soc. Perkin Trans 1. 1983, 2219, J. Het. Chem, 1981, 367, J. Org. Chem, 1968, 33, 4376, J. Het. Chem, 1983, 20, 385, Liebigs Annalen. Chem. 1992, 1281, EP 238319, Tetrahedron, 1981, 37, 3061, J. Org. Chem. 1958, 23, 1171, Pol. J. Chem. 1982, 50, 433, Tet. Letts,

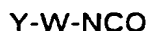
1981, 22, 2747, J. Org. Chem. 1989, 54, 5582, Liebigs Ann. Chem. 1994, 121, Tet. Letts. 1977, 2243, Tet. Letts. 1977, 2973 and by analogy to methods described for the preparation of substituted mandelic acids in for example J. Org. Chem. (1978), 43, (13), 2702; Org. Synth. (1945), 25, 33; Org. Synth. Col. Vol. IV, (1963), 110; Org. Synth. Col. Vol. I, (1941), 336-SE 7604030-2, Synthesis (1975), 163, Synth. Commun (1981), 11, 943; Org. Prep. Proced. (1970), 2, 249, EP 140454.

Compounds of formula II can also be obtained by reacting a compound of formula III with a compound of formula VI or by reacting a compound of formula XI



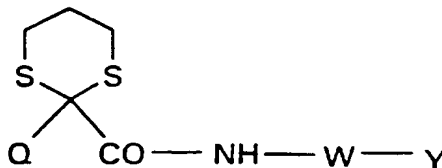
XI

first with a strong base, e.g. butyllithium and then with a compound of formula XII



XII

to give a compound of formula XIIIa



XIIIa

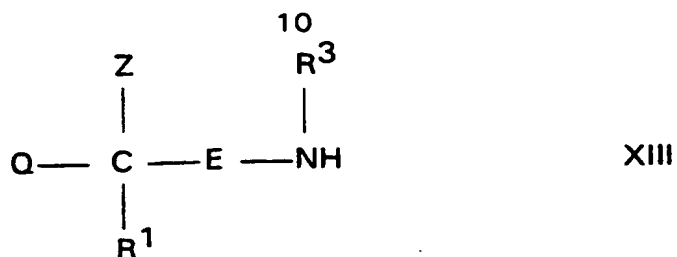
e.g. by the process described in D. Seebach, E.J. Corey. J. Org. Chem. 40, 231-237 (1975)) and the protecting dithianyl group is removed. e.g. by the method described by E.J. Corey, B.W. Erickson, J. Org. Chem. 36, 3553-3560, (1971).

Compounds of formula VI may be obtained by reacting the compound of formula VIb



with a dehydrating agent, such as triphosgene.

Compounds where W is $N(R^3)$, may be prepared also by reacting a compound of formula XIII



with a compound of formula XIV

Y-L

XIV

- Compounds where E is defined as under (ii) may be obtained from compounds where E is defined as under (i) by sulfurisation in known manner, e.g. using Lawesson's reagent or phosphorus pentasulfide, to give compounds of formula I where E is CS-N(R²).

- Compounds of formula I where E is defined as under (ii), W is optionally substituted methylene or ethylene and Q is optionally substituted phenyl are known, e.g. from WO 94/29267, or can be prepared by methods analogous to those described in that document.

- A compound of formula I, where E is defined under (ii), may be treated with a base followed by an optionally substituted alkyl or phenyl halide to give a compound where E is defined under (iii).

- When reacting compounds where Z is hydroxy or mercapto, it be advantageous to attach a protecting group to the hydroxy, e.g. a trimethylsilyl group which may subsequently be removed in conventional manner.

- Compounds of formula I may be modified in known manner to give other compounds of formula I where one of the groups is modified to another desired group. For example compounds of formula I, where Z is hydroxy can be treated to give compounds where Z has other desired values, e.g. by acylation or alkylation, in known manner.

- The invention is illustrated in the following Examples. Structures of isolated novel compounds were confirmed by elemental and/or other appropriate analyses.

- Temperatures are in °C.

Example 12-(3,5-Dichloro-2-thienyl)-N-[2-(3,4-dimethoxyphenyl)ethyl]-2-hydroxyacetamide

A solution of sodium borohydride (0.10 g) in water (6 ml) was added dropwise to a suspension of 2-(3,5-dichloro-2-thienyl)-N-[2-(3,4-dimethoxyphenyl)ethyl]-

- 5 2-oxoacetamide (2.0 g) in ethanol (60 ml). After removal of the solvent under reduced pressure, the residue was washed with water and extracted with ethyl acetate. The extract was dried over magnesium sulfate and concentrated under reduced pressure evaporated and the residue worked up to give the title compound as a gum. (Mol peak: M^+ : 390.29)

10 (Compound 1)

In a similar manner there was obtained

- a) 2-hydroxy-2-indol-3-yl-N-(2-phenylethyl)acetamide, gum (Compound 1a)

15 Example 2

A mixture of ethyl 2-hydroxy-2-(1-tritylimidazole-4-yl)-acetate (0.515 g) and 2-(3,4-dimethoxyphenyl)ethylamine (0.23 g) was heated at 120°C for 3 ½ hours. The mixture was cooled and purified by silica gel chromatography to give N-[2-(3,4-dimethoxyphenyl)ethyl]-2-hydroxy-2-(1-trityl-imidazole-4-yl)acetamide, foam.

20 (compound 2)

Example 3

To a solution of 2-hydroxy-2-(3-thienyl)acetic acid (5.0 g) in 1,2-dimethoxyethane (50 ml) at room temperature, there was added N-hydroxysuccinimide (3.63 g) followed by dicyclohexylcarbodiimide (6.51 g). The mixture was stirred for 30 minutes at room temperature. To this was added 2-(3,4-dimethoxyphenyl)ethylamine (5.35 ml) and 1,2-dimethoxyethane (5 ml). The mixture was stirred overnight at room temperature, filtered, the filtrate evaporated and the residue purified by silica gel column chromatography to give N-[2-(3,4-dimethoxyphenyl)ethyl]-2-hydroxy-2-(3-thienyl)acetamide, m.p. 110-4°.

30 (compound 3)

Example 4

Acetyl chloride (0.16 ml) was added dropwise to a solution of compound 3a (0.7 g) in dichloromethane (10 ml) containing triethylamine (0.31 ml), cooled to 0°. The mixture was stirred under nitrogen overnight and poured into aqueous sodium hydrogen carbonate. The mixture was extracted with ethyl acetate and the extract was dried and evaporated and the residue worked up to give 2-acetoxy-2-(6-chloro-3-pyridyl)-N-[2-(3,4-dimethoxyphenyl)ethyl]-acetamide, as a gum. (compound 4)

10 Example 5

N-[2-(3,4-dimethoxyphenyl)ethyl]formamide (3.135 g) and dry triethylamine (4.6 ml) in dry dichloromethane (15 ml) was stirred with cooling in ice water whilst triphosgene (1.6 g) and dichloromethane (10 ml) was added dropwise. The mixture was stirred for 4 hours at 5°C and then cooled to -78°C. A solution of titanium tetrachloride (1.65 ml) in dry dichloromethane (30 ml) was added and the mixture stirred for 2 hours allowing the temperature to rise to -40°C. Thiophene-2-carbaldehyde (1.4 ml) in dry dichloromethane (10 ml) was added dropwise and the mixture allowed to rise to room temperature. The mixture was stirred overnight and 5N hydrochloric acid (8 ml) was added. The mixture was stirred for 1.5 hours and the organic layer separated, washed with water, dried and evaporated. The residue was purified by silica gel chromatography to give 2-(2-thienyl)-N-[2-(3,4-dimethoxy-phenyl)ethyl]-2-hydroxyacetamide, m.p. 106-8°C. (Compound 5)

25 Example 6

Bromine (0.55 ml) was added to a solution of Compound 3 (3.46 g) in acetic acid (70 ml). The mixture was stirred for room temperature overnight, poured into water, neutralised with aqueous sodium hydrogen carbonate and extracted with ethyl acetate. The extract was washed with brine, dried and evaporated and the residue subjected to silica gel chromatography to give

a) 2-acetoxy-N-[2-(2-bromo-4,5-dimethoxyphenyl)ethyl]-2-(3-thienyl)acetamide, m.p. 137-9° (Compound 6a)

b) N-[2-(2-bromo-4,5-dimethoxyphenyl)ethyl]-2-(2-bromo-3-thienyl)-2-hydroxyacetamide, gum, (Compound 6b)

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c) N-[2-(2-bromo-4,5-dimethoxyphenyl)ethyl]-2-(3-thienyl)-2-hydroxyacetamide, m.p. 148-9°. (Compound 6c), and

d) 2-bromo-N-[2-(2-bromo-4,5-dimethoxyphenyl)ethyl]-2-(3-thienyl)acetamide, m.p. 165-7. (Compound 6d)

5

Preparation of starting materials

2-(3,5-Dichloro-2-thienyl)-N-[2-(3,4-dimethoxy-phenyl)ethyl]-2-oxoacetamide

A solution of 3,5-dichloro-2-thiophene-2-oxoacetyl chloride (4.66 g) in toluene (15 ml) was added dropwise, at room temperature, to a mixture of 2-(3,4-dimethoxyphenyl)ethylamine (3.47 g) in toluene (35 ml). The mixture heated up to 53°. After a short time a precipitate of triethylammonium chloride appeared. After stirring for 2 hours, the mixture was filtered, the precipitate was washed with toluene and the toluene phase concentrated under reduced pressure. The residue was extracted with ethyl acetate and the extract washed with water, dried over magnesium sulfate and evaporated under reduced pressure. The residue was recrystallised from ethanol to give the title compound, m.p. 128° (Mol peak: M^+ : 388.27).

20 2-hydroxy-2-(3-thienyl)acetic acid

Method 1

To an ice cold solution of lithium bromide (46.5 g) and potassium hydroxide (31.3 g) in water (130 ml) was added dioxane (130 ml) and bromoform (71.3 g), followed by 3-thiophenecarbaldehyde (31.7 g). The mixture was stirred for 24 hours at room temperature, filtered and the precipitate washed with ether and suspended in a water ether mixture and acidified with hydrochloric acid. The ether layer was worked up to give the title compound, m.p. 104-6°.

Method 2

30 3-Thiophenecarbaldehyde (25 g) was added to a solution of sodium cyanide (14.2 g) in water (60 ml). Saturated aqueous sodium bisulfite (70 ml) was added together with ice (60 g) to keep the temperature below 30°. The mixture was allowed to stand overnight and the organic layer added to hydrochloric acid (9N; 100 ml). The mixture was stirred for 12 hours at room temperature. The aqueous

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lay r was extracted with ether and the extract worked up to give the title compound.

2-(6-chloro-3-pyridyl)-2-hydroxyacetic acid

- 5 6-Chloro-3-pyridylcarbonyl chloride (12 g) was dissolved in diglyme (68 ml) and cooled to -78°C under nitrogen. To this solution was added a 0.5 M solution of lithium aluminium tri-tert.-butoxyhydride in diglyme (135 ml), dropwise, over 1 ½ hours, maintaining the temperature at -70°C. The mixture was stirred for one hour and poured into a mixture comprising concentrated hydrochloric acid (20 ml)
- 10 saturated aqueous ammonium chloride (40 ml) and ice (20 g). The mixture was stirred and then silica was added. The mixture was stirred with ethyl acetate (100 ml) and left overnight under nitrogen with cooling. The mixture was filtered, the silica pad was washed with ethyl acetate and the combined organic materials were washed with water and aqueous sodium hydrogen carbonate, dried and
- 15 evaporated under reduced pressure to give 6-chloro-3-pyridylcarbaldehyde.

- This product (7.3 g) was dissolved in ethanol (45 ml) and malononitrile (3.25 ml) was added and washed in with ethanol (5 ml). Piperidine (3 drops) was added and the mixture heated to reflux for 2 to 3 minutes. The mixture was allowed to cool
- 20 to room temperature and then stirred for one hour. The mixture was filtered and washed with diethyl ether to give (6-chloro-3-pyridylmethyl-idene)malononitrile. This product (0.76 g) was dissolved in acetonitrile (10 ml) over sulphuric acid (0.1 ml) was added. Diluted aqueous sodium hypochlorite (7.5 ml) was added in 0.5 ml portions with the pH being adjusted to 5, using 0.2 normal sulphuric acid after
- 25 each portion. The mixture was added to water and stirred at room temperature for 45 minutes. It was filtered to give 2-chloro-5-(3,3-dicyanooxiran-2-yl)pyridine. A mixture of this product (3.0 g), dioxane (70 ml) and water (20 ml) was heated under nitrogen under reflux overnight. The mixture was concentrated under reduced pressure and the residue dissolved in water and washed with ether. The
- 30 solution was evaporated to dryness to give the title compound, mp. 48-50°.

Ethyl 2-(1-tritylimidazole-4-yl)-2-hydroxyacetate

Ethyl magnesium bromide (3 molar in ether; 2.1 ml) was added to a stirred solution under nitrogen of 1 trityl-4-iodoimidazole (2.5 g). The mixture was cooled

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to 0° and a mixture of copper cyanide and lithium chloride (1:2; 1 molar in tetrahydrofuran; 5.8 ml) was added. The mixture was stirred for 15 minutes and then cooled to -46°. A solution of ethyl chloroformate (0.5 ml) in dichloromethane (4 ml) was added dropwise. The mixture was allowed warm to room temperature and stirred overnight. Dichloromethane (50 ml) was added and the mixture quenched with saturated aqueous ammonium chloride and a few drops of ammonia. The aqueous layer was extracted with dichloromethane and the extracts worked up to give ethyl 2-(1-tritylimidazole-4-yl)-2-oxoacetate, as a brown solid.

10

To a stirred solution of this product (2.1 g) in dry tetrahydrofuran (40 ml) and dry ethanol (20 ml) was added sodium borohydride (1 g). The mixture was stirred for one hour at room temperature and evaporated to dryness. A mixture of ethyl acetate (100 ml) and water (30 ml) was added and the ethyl acetate layer collected, dried and worked up to give the title compound.

15

2-(3-bromo-4,5-dihydroisoxazol-5-yl)-2-hydroxyacetic acid

N-bromosuccinimide (4.094 g) was added to a solution of hydroxyiminoacetic acid (1.012 g) in dimethoxyethane (15 ml) and water (2.25 ml) at 0°. The mixture was stirred for a few hours at room temperature and kept at 0° overnight. It was then added dropwise to a solution of ethyl 2-hydroxybut-3-enoate, and potassium hydrogen carbonate (4.6 g) in dimethoxyethane (7.5 ml). The mixture was stirred at room temperature overnight, partitioned between dichloromethane and water and the organic phase worked up to give ethyl acetate. The extract was dried and evaporated and the residue worked up to give ethyl 2-(3-bromo-4,5-dihydroisoxazol-5-yl)-2-hydroxyacetate.

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Lithium hydroxide monohydrate (0.25 g) was added to a solution of this (0.5 g) in tetrahydrofuran (1 ml) and water (3 ml) at 0°. The mixture was stirred for 1 ½ hours at room temperature, acidified with hydrochloric acid and extracted with ethyl acetate. The extract was washed with brine, dried and evaporated to give the title product, which solidified on standing.

Example 7

Lawesson's reagent (2,4-bis(4-methoxyphenyl)-1,2,3,4-dithiadiphosphetane 2,4-disulphide; 2.6 g) was added to a solution of N-[2-(4-ethoxy-3-methoxy-phenyl)ethyl]-O-trimethylsilyl-3,4-dichloromandelamide (5.4 g) in dry
5 tetrahydrofuran (100 ml). The mixture was heated under reflux for 1 hour, evaporated and the residue purified by silica gel column chromatography to give N-[2-(4-ethoxy-3-methoxyphenyl)ethyl]-O-trimethylsilyl-3,4-dichloromandelothioamide, as an oil (compound 7);

10 Preparation of the starting material

A solution of trimethylsilyl chloride (1.6 ml) in tetrahydrofuran (20 ml) was added to a stirred solution of N-[2-(4-ethoxy-3-methoxyphenyl)ethyl]-3,4-dichloro-mandelamide (5 g) and triethylamine (18 ml) in tetrahydrofuran (80 ml). The mixture was stirred at room temperature overnight and the tetrahydrofuran
15 evaporated. Water was added and the mixture extracted with ethyl acetate. The extract was washed with water and brine, dried and evaporated to give N-[2-(4-ethoxy-3-methoxy-phenyl)ethyl]-O-trimethylsilyl-3,4-dichloromandelamide, as an oil, which was used without further purification.

20 Example 8

A solution of methyl 2-(3,4-dichlorophenyl)-2-hydroxyacetate (7.0 g) and methylhydrazine (7.0 ml) in ether (50 ml) was stirred at room temperature for 5 hours. The product was filtered, washed with ether and dried to give N'-methyl-3,4-dichloromandelohydrazide, m.p. 169-70°. (compound 8)

25

In a similar manner there was also obtained

- a) N'-methyl-4-chloromandelohydrazide, m.p. 161-4° (compound 8a), and
- b) N'-methyl-4-(trifluoromethyl)mandelohydrazide, m.p. 157-9°, (compound 8b), and

- 30 c) 4-chloromandelohydrazide, m.p. 184-6° (compound 8c).

Example 9

A solution of compound 8 from Example 8 (1.33 g), 3,4-dimethoxybenzyl chloride (1.0 g) and N,N-diisopropylethylamine (0.75 g) in acetonitrile (50 ml) was heated

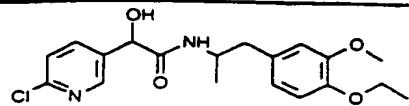
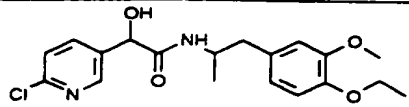
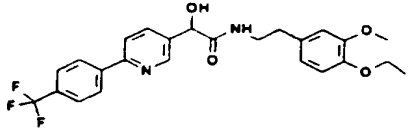
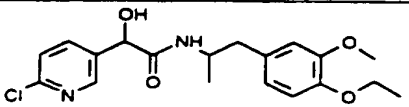
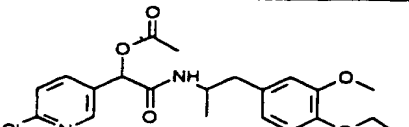
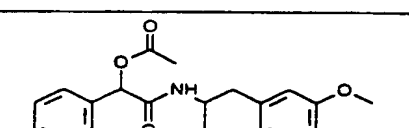
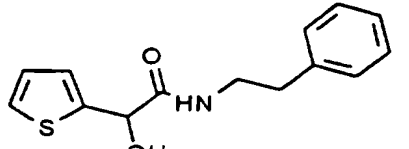
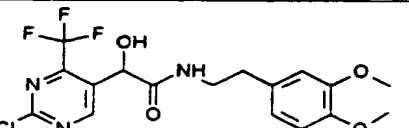
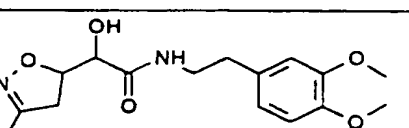
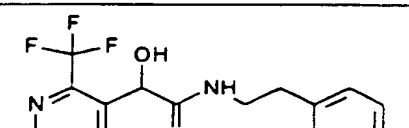
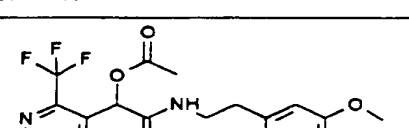
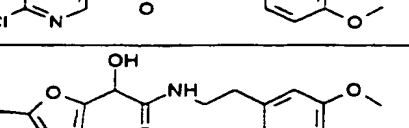
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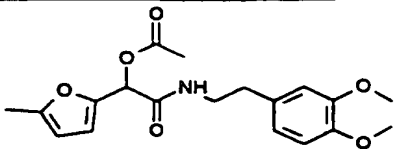
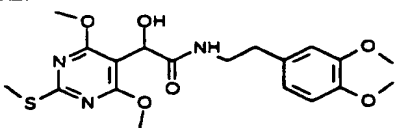
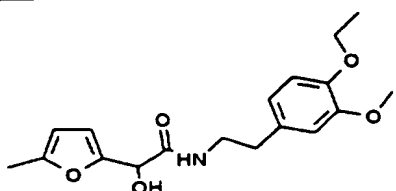
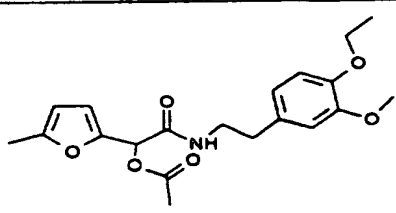
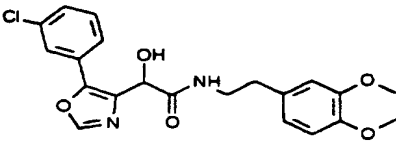
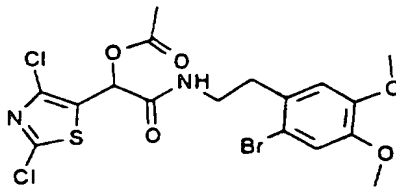
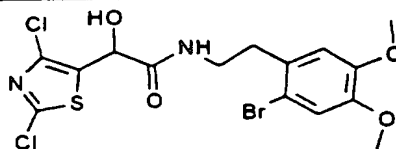
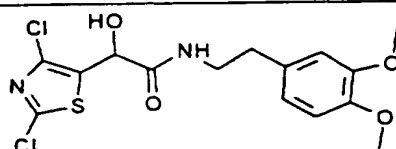
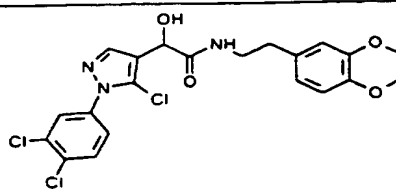
under reflux for 8 hours. Solvent was removed under reduced pressure and the residual gum taken up in ethyl acetate. The solution was washed with water, dried over magnesium sulfate, and concentrated to a gum which was purified by silica gel chromatography using ethyl acetate/methanol (20:1), to give

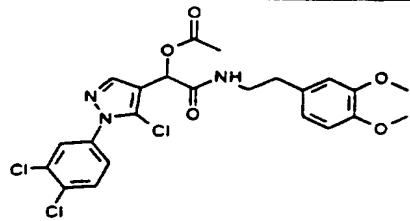
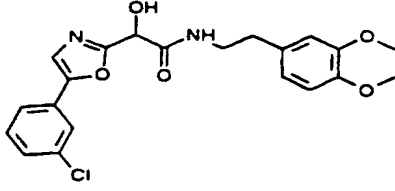
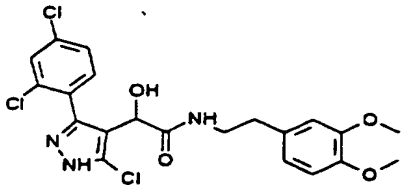
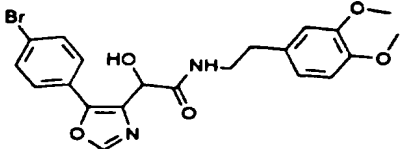
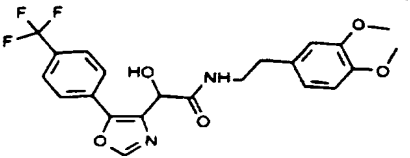
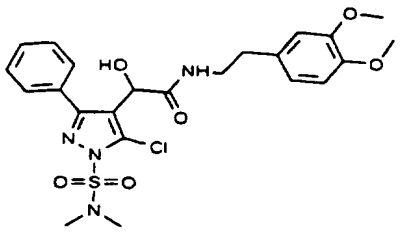
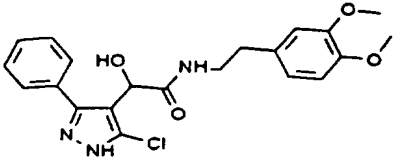
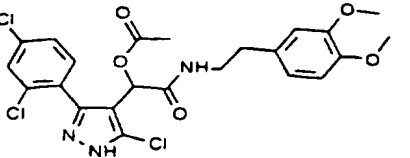
- 5 N'-(3,4-dimethoxybenzyl)-N'-methyl-3,4-dichloromandelohydrazide as a thick colourless gum. (compound 9)

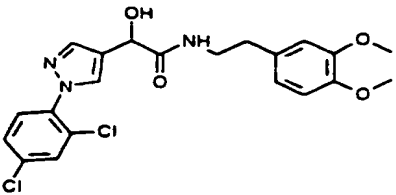
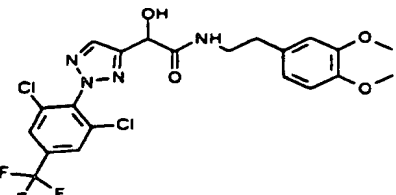
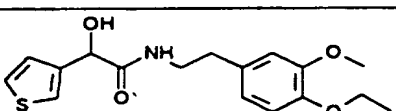
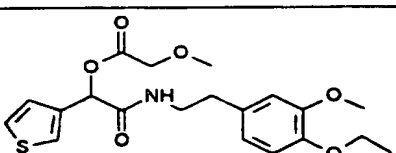
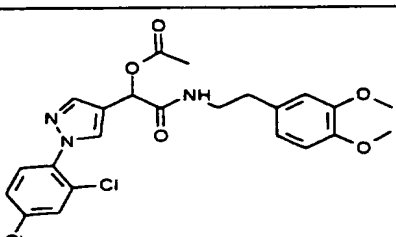
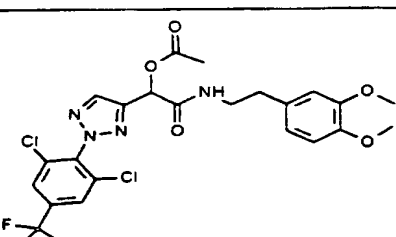
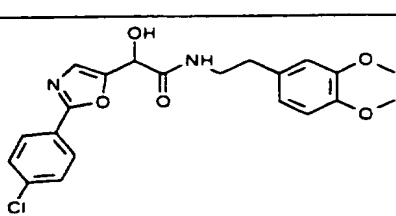
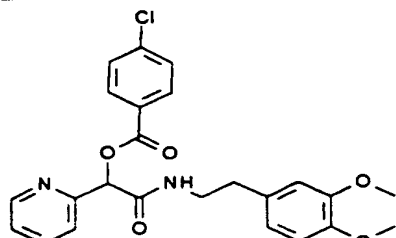
The following tables illustrates further compounds of the invention which are obtained by the methods previously described.

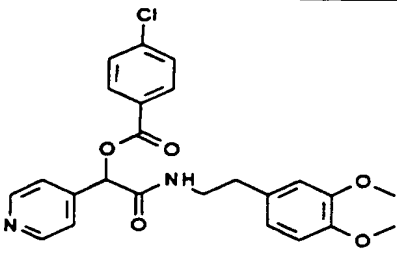
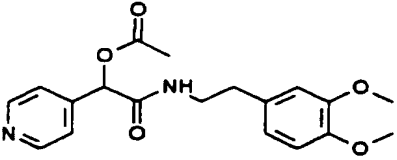
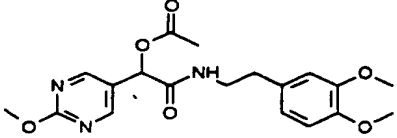
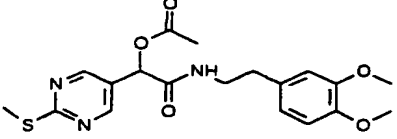
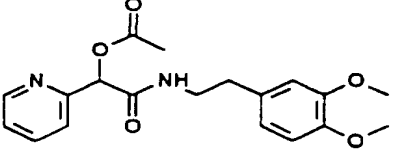
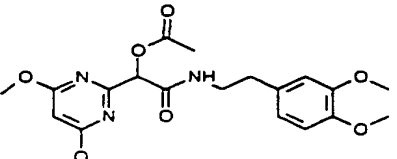
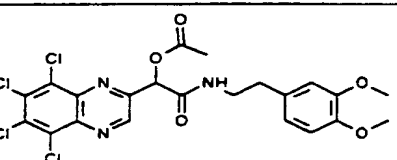
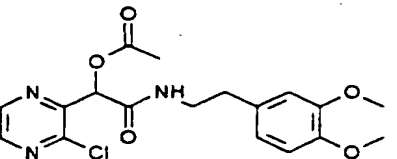
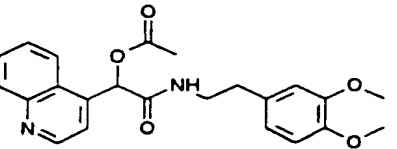
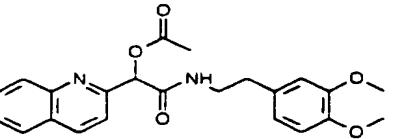
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12		oil
13		184-5
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15		62-3
16		oil
17		oil
18		137-41
19		oil
20		oil
21		gum

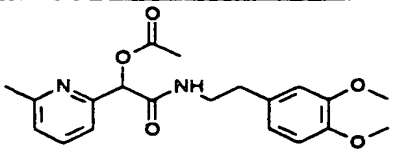
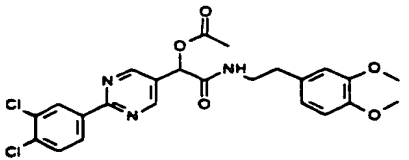
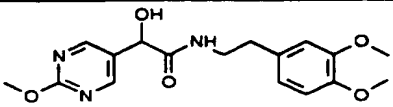
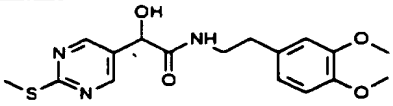
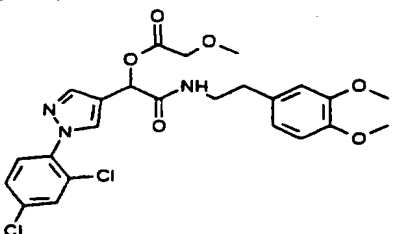
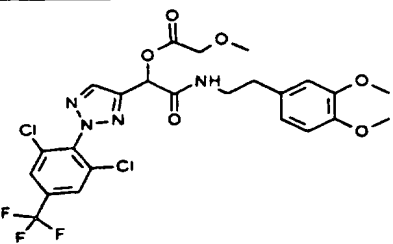
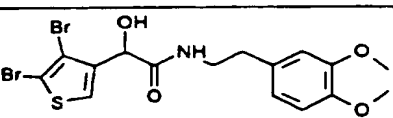
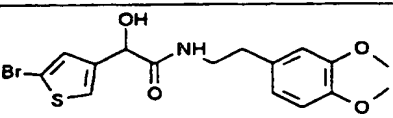
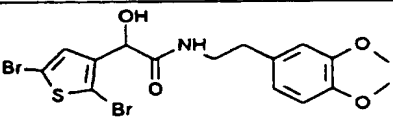
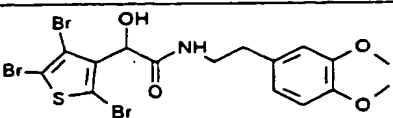
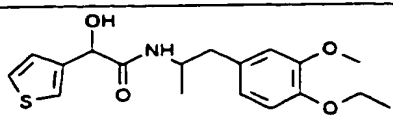
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31		oil
32		oil
33		117-19

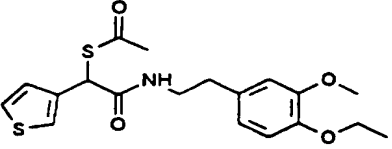
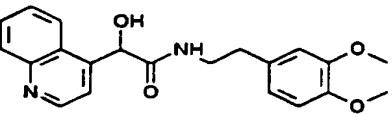
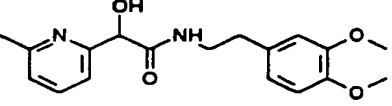
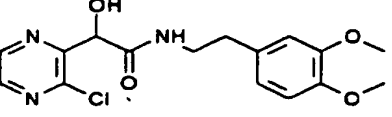
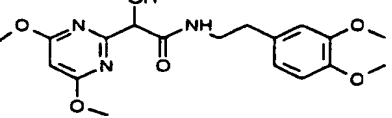
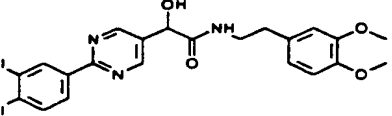
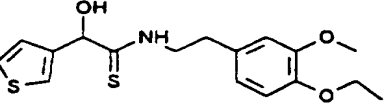
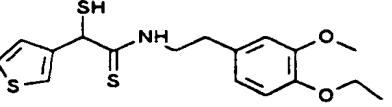
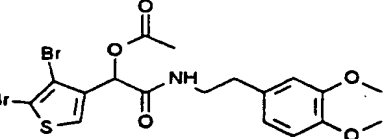
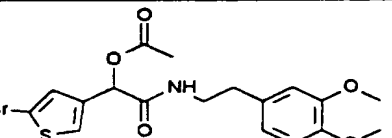
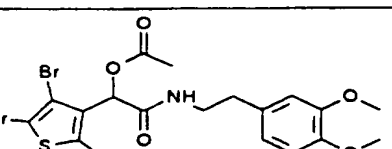
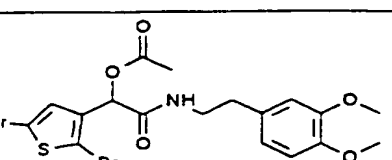
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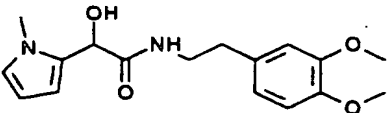
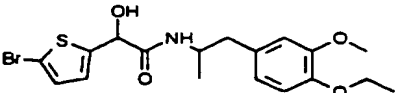
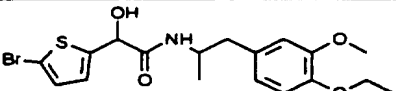
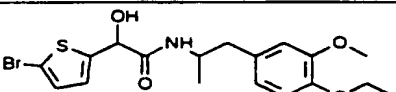
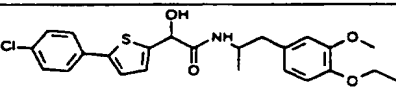
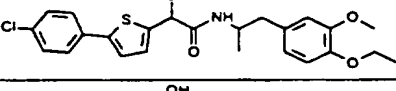
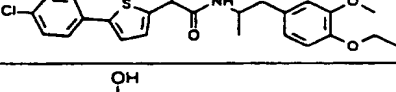

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49		oil
50		107-10

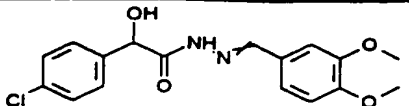
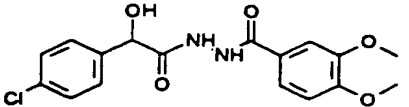
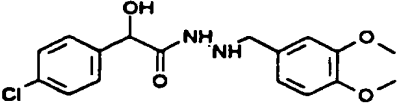
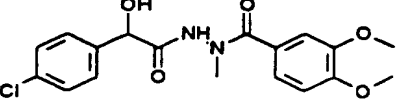
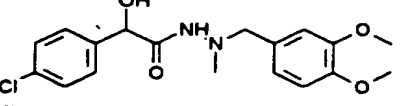
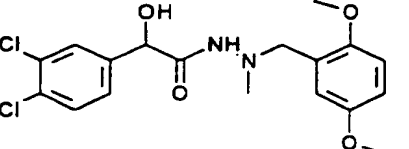
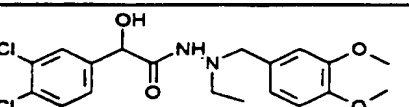
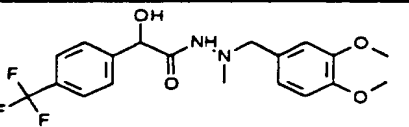
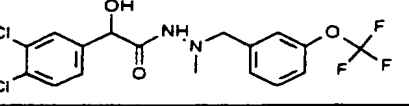
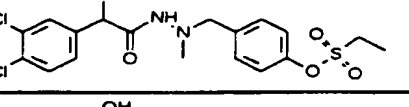
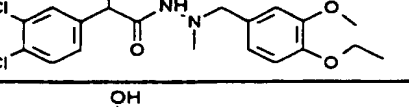
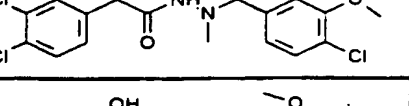
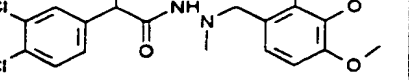
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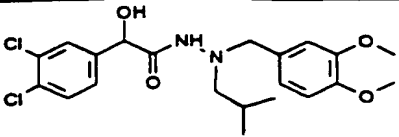
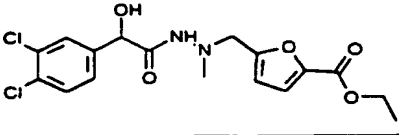
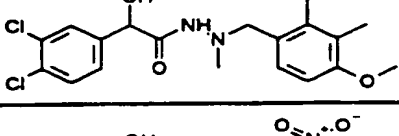
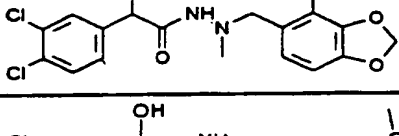
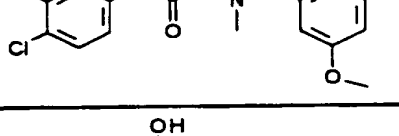
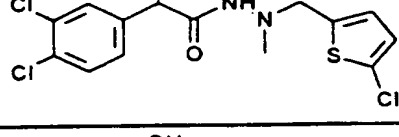
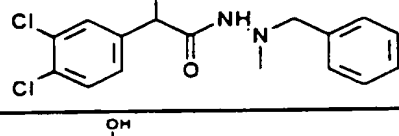
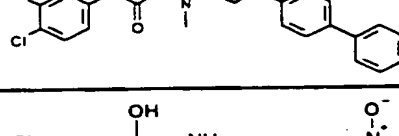
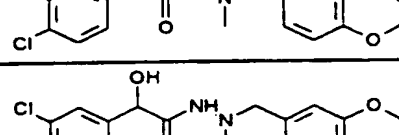
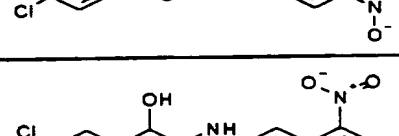
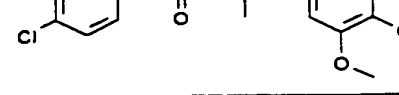
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67		154-6
68		oil

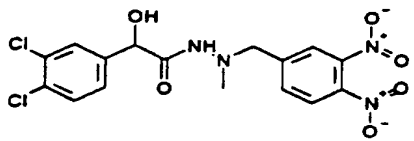
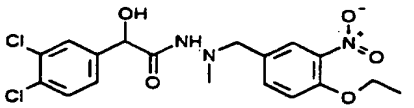
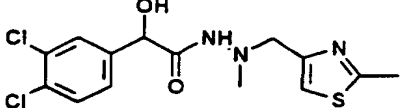
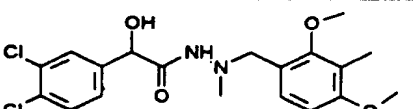
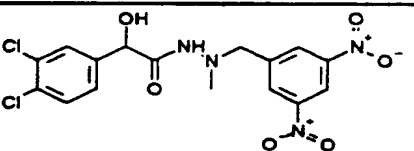
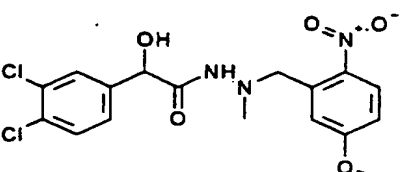
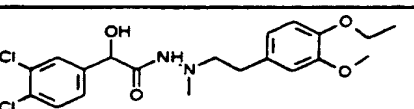
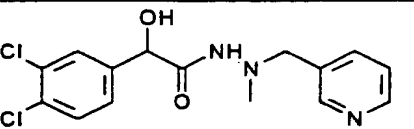
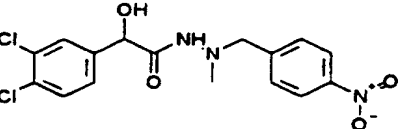
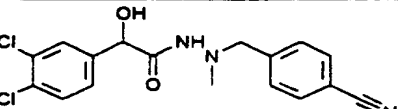
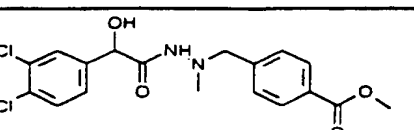
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71		oil
72		oil
73		oil
74		oil
75		132-33
76		97-9
77		oil
78		145-7
79		oil

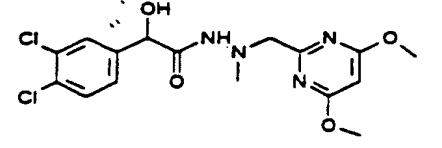
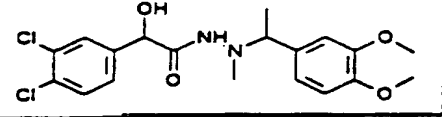
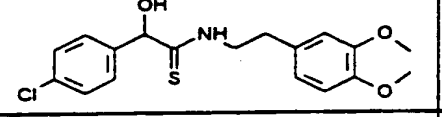
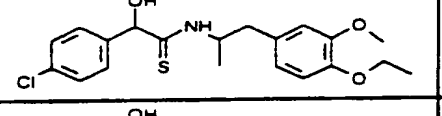
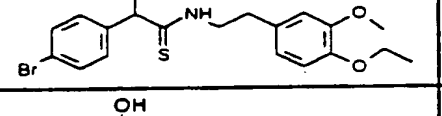
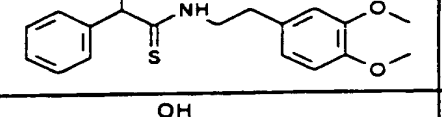
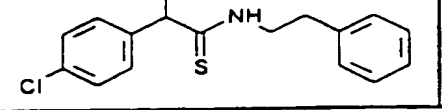
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82		oil
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84		oil
85		165-7
86		oil
87		oil
88		101-3
89		oil
90		oil
91		oil

92		111-13
93		oil
94		oil
95		oil
96		oil
97		oil
98		oil
99		oil

100		145-8
101		132-5
102		123-6
103		223-5
104		oil
105		129.7-30.2
106		oil
107		117-19
108		oil
109		88.7.-90.3
110		oil
111		oil
112		oil

113		oil
114		oil
115		116.4-17.6
116		137.2-38.7
117		oil
118		oil
119		91.6-2.5
120		136.8-37.5
121		117.7-18.6
122		127.8-29.4
123		170.9-2.10

124		73.7-5.6
125		128.6-30.2
126		oil
127		oil
128		58.8-62-4
129		oil
130		oil
131		126-29
132		124-26
133		oil
134		oil

135		oil
136		oil
137		oil
138		oil
139		oil
140		oil
141		oil

Example 10

A mixture of 5-(4-chlorophenyl)-2,2-dimethyl-1,3-dioxolan-4-one (2.26 g) and O-(2-nitrobenzyl)hydroxylamine (1.7 g) was heated under reflux for 24 hours. It was cooled and evaporated and the residue purified by silica gel column chromatography (eluent: ethyl acetate/hexane; 1:3) to give 4-chloro-N-(2-nitrobenzyloxy)-mandelamide. m.p. 93-4°. (compound 10a)

Example 11

A mixture comprising a solution of mandelic acid (3 g) in dichloromethane (40 ml), a catalytic amount of 4-(dimethylamino)pyridine, pyridine (3.24 g) and trimethylsilyl chloride (4.5 g) was stirred at room temperature for 3 hours.

The mixture was cooled to 0°, and 10 drops of dimethylformamide added, followed by oxalyl chloride (2.58 g). The mixture was stirred for 1 hour at this temperature and allowed to warm to room temperature. It was stirred for 15 minutes and cooled to 0°. A solution of O-benzylhydroxylamine hydrochloride (3.46 g) in pyridine (3.24 g) and dichloromethane (30 ml) was added and the mixture was stirred overnight at room temperature. Citric acid (4.14 g) in methanol (30 ml) was added and the mixture was stirred for 30 minutes, diluted with ethyl acetate (100 ml) washed with dilute hydrochloric acid and water, dried and evaporated and the residue worked up to give N-benzyloxymandelamide. m.p. 101-3°. (compound 11a)

Example 12

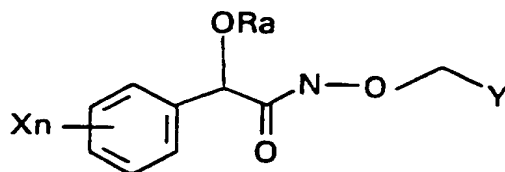
To a solution of compound 4.1 (1.5 g) in dichloromethane (50 ml) at room temperature, there was added triethylamine (0.89 ml) followed by acetyl chloride (0.46 ml). The mixture was stirred for 1 hour at room temperature, washed with
5 water, dried and evaporated and the residue purified by silica gel column chromatography to give residue worked up to give O-acetyl-N-benzyloxymandelamide. m.p. 121-3°. (compound 12a)

Example 13

10 To a solution of 4-chloromandelic acid (3.0 g) in 1,2-dimethoxyethane (35 ml) at room temperature, there was added N-hydroxysuccinimide (1.85 g) followed by dicyclohexylcarbodiimide (3.32 g). The mixture was stirred for 45 minutes at room temperature. To this was added a solution of O-benzylhydroxylamine hydrochloride (2.81 g) and N,N-diisopropyl-ethylamine (3.1 ml) in 1,2-dimethoxyethane (30 ml),
15 which had been prestirred for 1 ½ hours and filtered. The mixture was stirred overnight at room temperature, filtered, the filtrate evaporated and the residue purified by silica gel column chromatography to give N-benzyloxy-4-chloromandelamide. m.p. 132-4°. (compound 13a)

Example 14

In a similar manner to the appropriate method described in Examples 3-6, the following compounds were obtained.



5	Cpd	Xn	Ra	Y	m.p.(°)
	14.1	4-Cl	H	3,4-(MeO) ₂ -Ph	105-7
	14.2	3,4-Cl ₂	H	4-EtO,3-MeO-Ph	oil
	14.3	4-CF ₃	H	4-EtO,3-MeO-Ph	86-8
10	14.4	4-Cl	COMe	3,4-(MeO) ₂ -Ph	oil
	14.5	3,4-Cl ₂	COMe	4-EtO,3-MeO-Ph	oil
	14.6	4-CF ₃	COCH ₂ Cl	4-EtO,3-MeO-Ph	oil
	14.7	4-Cl	COMe	Ph	oil

Test Example

Compounds are assessed for activity against one or more of the following:

Phytophthora infestans: late tomato blight

Plasmopara viticola: vine downy mildew

5 *Pyricularia oryzae*: rice blast

Botrytis cinerea: grey mould

Venturia inaequalis: apple scab

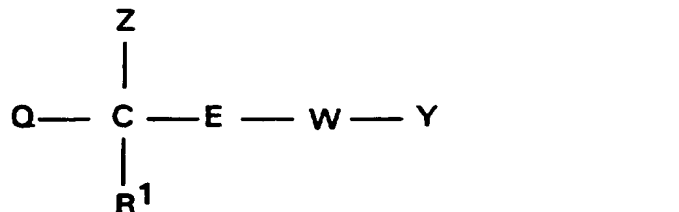
Leptosphaeria nodorum: glume blotch

10 Aqueous solutions or dispersions of the compounds at the desired concentration, including a wetting agent, were applied by spray or by drenching the stem base of the test plants, as appropriate. Plants or plant parts were then inoculated with appropriate test pathogens and kept under controlled environment conditions suitable for maintaining plant growth and development of the disease. After an appropriate time, the degree of infection of the affected part of the plant was
15 visually estimated. Compounds were considered active if they gave greater than 50% control of the disease at a concentration of 500 ppm (w/v) or less.

Compounds 7, 8c, 10, 13, 17, 18, 23, 25, 27, 38, 40, 57, 75-78, 89, 90, 93-99, 101, 104, 106-11, 113, 115, 119-21, 123, 126, 127, 136, 138, 139, 10a,
20 14.1 and 14.2 showed activity against *Phytophthora infestans*;
Compounds 3, 4, 6a-d, 7, 8a, 8c, 9, 11-14, 17-20, 22-27, 31, 32, 34-37, 43, 46, 48, 50, 52, 57, 58, 69, 71, 75-77, 79, 82, 84-87, 89, 90, 92, 94-99, 102-10, 112, 113, 115-7, 119, 121-4, 126-8, 131, 137-9, 10a, 12a, 14.1, 14.2 and 14.3 showed activity against *Plasmopara viticola*;
25 Compounds 6b, 13, 14, 90 and 130 showed activity against *Pyricularia oryzae*
Compounds 19, 29, 50 and 56 showed activity *Botrytis cinerea*;
Compounds 6a, 6b, 6d, 27, 90, 103 and 124 showed activity against *Venturia inaequalis*, and
Compounds 8c, 41 and 104 showed activity against *Leptosphaeria nodorum*.

35
CLAIMS

1. The use for combating phytopathogenic fungi, of a compound of formula I



- 5 wherein

Q is optionally substituted heterocyclyl;

Z is optionally substituted hydroxy or mercapto;

E is (i) $\text{CO}-\text{N}(\text{R}^2)$, (ii) $\text{CS}-\text{N}(\text{R}^2)$ or (iii) $\text{C}(\text{SR}^2)=\text{N}$

W is O, $\text{N}(\text{R}^3)$, optionally substituted methylene or ethylene;

- 10 R^1 , R^2 and R^3 are phenyl or alkyl, each of which is optionally substituted, or hydrogen;

Y is phenyl, heteroaryl or alkyl, each of which is optionally substituted, or hydrogen;

and when W is O or $\text{N}(\text{R}^3)$, and/or E is (ii) or (iii), Y is also optionally substituted

- 15 phenyl, together with salts and complexes with metal salts.

- 2 Compounds of general formula I as defined in claim 1 with the exception that when E is defined as in (i), W is NH, R^1 is H and Y is hydrogen, then Q is substituted.

20

3. Fungicidal compositions which comprise a compound as defined in claim 1 or 2 in admixture with an agriculturally acceptable diluent or carrier.

4. A method of combating phytopathogenic fungi at a locus infested or liable to be infested therewith, which comprises applying to the locus a compound as defined in claim 1 or 2.
- 25

INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 95/02849

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6	C07D333/28	A01N43/10	A01N43/40	A01N43/42	A01N43/54
	A01N43/08	A01N43/26	C07D333/24	C07D209/18	C07D233/54
	C07D213/61	C07D239/30	C07D239/60	C07D239/40	C07D239/36

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 071 568 (CIBA GEIGY AG) 9 February 1983 see page 61 - page 66; claims 1,4,14-16; table 5 ---	1-3
X	DATABASE WPI Week 8906 Derwent Publications Ltd., London, GB; AN 89-042265 & JP,A,63 313 773 (TOKUYAMA SODA KK) , 21 December 1988 see abstract ---	1-3
P,X	DE,A,43 19 887 (HOECHST SCHERING AGREVO GMBH) 22 December 1994 see claims -----	1-3

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *&* document member of the same patent family

Date of the actual completion of the international search

21 March 1996

Date of mailing of the international search report

29. 03. 96

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INTERNATIONAL SEARCH REPORT

Final Application No

PCT/GB 95/02849

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 95/02849

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0071568	09-02-83	AU-B- 550357	20-03-86
		AU-B- 8445982	09-12-82
		CA-A- 1198438	24-12-85
		GB-A,B 2104065	02-03-83
		US-A- 4663463	05-05-87
		JP-B- 2061459	20-12-90
		JP-A- 58015960	29-01-83

DE-A-4319887	22-12-94	AU-B- 7123994	03-01-95
		WO-A- 9429267	22-12-94
